Remarks

Claims 49, 50, 52, 53, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76 and 77 are pending. Claims 76 and 77 have been cancelled without prejudice. Claims 50, 70 and 72 have been amended to remove the recitation of the phrase "blood sample which comprises leukocytes which have not been fractionated into cell types", without prejudice. Claims 63 and 64 have been newly cancelled without prejudice. Claim 65 has been amended to remove its dependency from newly cancelled claim 63. Claim 71 has been amended to include the recitation of "$p<0.5$".

Support for these amendments are found throughout the specification and in the claims as originally filed. No new matter has been entered. All newly added claims are encompassed by Group I of the restriction requirement drawn to methods of identifying biomarkers for osteoarthritis and methods for diagnosis/classification of osteoarthritis, further restricted to a DMN gene.

Claims Rejection - 35 U.S.C. 112 1st written description

Claims 50, 52, 53, 56, 57, 58, 70, 72, 76 and 77 are rejected under 35 U.S.C. 112, 1st paragraph, as failing to comply with the written description requirement.

Claims 50, 70 and 72 and dependent claims are rejected on the grounds that the instantly recited phrase "comprises leukocytes which have not been fractionated into cell types" is new matter. Although Applicant respectfully traverses, Applicant has amended the instant claims by removing the recitation of the phrase "a blood sample which comprises leukocytes which have not been fractionated into cell types" from the instant claims without prejudice.

Claims 76 and 77 are rejected on the grounds that the negative proviso "wherein none of said control subjects is selected from the group consisting of….." is new matter. Applicant respectfully traverses, but in the interest of advancing prosecution has cancelled claims 76 and 77 without prejudice, thereby rendering the instant rejection of these claims moot.

In light of the comments and claim amendments, Applicant respectfully requests reconsideration and withdrawal of the instant rejections.

Claims Rejection - 35 U.S.C. 112 1st enablement

Claims 49, 50, 52-53, and 56-57 are rejected under 35 U.S.C. 112, 1st paragraph, as failing to comply with the enablement requirement.

Applicant respectfully traverses. Applicant disagrees with the rejection's assertion that the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention in view of the breadth of the claims, the amount of guidance provided by the specification and the level of predictability in the art.

The rejected claims include the steps of determining the level of RNA encoded by a DMN gene in a blood sample obtained from a human test subject and comparing it to the level of control RNA encoded by the DMN gene in blood samples of control subjects, wherein the comparison is indicative of osteoarthritis in said human test subject.

Independent claim 59 is drawn to a method of detecting expression of a desmuslin (DMN) gene in a human test subject comprising detecting RNA encoded by the gene in a blood sample of the test subject, using an oligonucleotide of predetermined sequence which is specific only for RNA encoded by said gene in said sample, and/or for cDNA complementary to RNA encoded by said gene in said sample.

Independent claim 68 is drawn to a method of screening a human test subject for being a candidate for having osteoarthritis, said method comprising: (a) detecting RNA encoded by a desmuslin (DMN) gene in a blood sample of said test subject, using an oligonucleotide of predetermined sequence which is specific only for RNA encoded by said gene in said sample, and/or for cDNA complementary to RNA encoded by said gene in said sample; and-(b) quantifying a level of RNA encoded by said gene in said sample of said test subject; and-(c) comparing said level of RNA in said sample of said test subject to a quantified level of control RNA encoded by said gene in blood samples of control subjects classified as healthy subjects, wherein said test subject is a candidate for having osteoarthritis if said level of RNA encoded by said gene in said blood sample of said human test subject is significantly different relative to that of said control subjects classified as healthy subjects with a p value less than 0.05.

Independent claim 71 is drawn to a method of classifying expression of a desmuslin (DMN) gene in a human test subject, said method comprising: (a) quantifying a level of RNA

encoded by said gene in a blood sample of said test subject; and (b) comparing said level of step (a) with quantified levels of RNA encoded by said gene in blood samples of control subjects classified as having osteoarthritis; and (c) comparing said level of step (a) with quantified levels of RNA encoded by said gene in blood samples of control subjects classified as healthy subjects; wherein a determination from steps (b) and (c) that said level of step (a) is statistically similar to said levels in said samples of said subjects classified as having osteoarthritis and is statistically different relative to said levels in said samples of said subjects classified as healthy subjects, results in a classification of expression of said gene in said test subject with that of said subjects classified as having osteoarthritis, and wherein a determination from steps (b) and (c) that said level of step (a) is statistically different relative to said levels in said samples of said subjects classified as having osteoarthritis and is statistically similar to said levels in said samples of said subjects classified as healthy subjects, results in a classification of expression of said gene in said test subject with that of said subjects classified as healthy subjects.

The Office Action indicates on pages 5-6, that the claims all set forth comparing the test level to a quantified level of RNA encoded by said gene in blood samples from control subjects, but the specification does not provide this quantified level, which the office action contends is necessary to the understanding of the relationship between DMN expression and osteoarthritis. The Office Action further states that the nature of the difference between the test and controls is not disclosed, with respect to the level and direction of the difference, and the finding was not replicated.

Applicant submits that neither the magnitude or direction of the expression of the DMN, i.e., the "nature of the 'difference,'" are absolutely required to enable, i.e., teach, one of ordinary skill in the art how to make and/or use the claimed invention. Instead, what is required is at least one method for enabling the invention, which is provided in the way of identifying statistically significant differentially expressed genes at a threshold of $p<0.05$.

Applicant respectfully submits that DMN is differentially expressed in blood of samples from individuals with osteoarthritis versus healthy control subjects, Applicant has provided those of skill in the art one method, albeit not necessarily an exclusive method, to aid in identifying a likelihood of osteoarthritis (e.g., relative to a likelihood of being healthy). It will be appreciated that as long as the specification discloses ***at least one method*** for making and using the claimed

invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. See In re Fisher, 427 F.2d 833, 839 (CCPA 1970). Failure to disclose other methods (e.g., determination of magnitude and/or direction) by which the claimed invention may be made does ***not*** render a claim invalid under Section 112. See Spectra-Physics, Inc. v. Coherent, Inc. 827 F.2d 1524, 1533 (Fed. Cir.), *cert. Denied*, 484 U.S. 954 (1987). Moreover, the fact that Applicant has exemplified specific genes which are differentially expressed in patients with osteoarthritis versus healthy controls with a p value of less than 0.05 from thousands of genes screened and with values that are often much lower than 0.05, is the nexus of the invention, and knowledge of the direction or magnitude of the differential expression is not required to practice the claims.

Indeed, methods and protocols for applying differentially expressed genes to indicate the presence of a disease or condition, ***regardless of direction of change of expression***, are well established in the art and disclosed and incorporated by reference in the specification. For example, Slonim DK, Nature Genetics Supplement, Vol. 32, 502-8 (2002), which is incorporated by reference in the instant specification at paragraph 135 of the published application (2004/0248170), states that "***[t]he most basic question one can ask in a transcriptional profiling experiment is which genes' expression levels changed significantly***." Applicant respectfully submits that Table 3O, in fact, provides which genes' expression levels—including DMN (p value of 4.14555E-05)—changed significantly; and thus, the specification comports with the methods and protocols generally accepted in the art. Submitted herewith is a copy of Slonim, which the Office is kindly asked to make of record.

The Applicant respectfully submits that the invention is taught by the specification and claimed in such terms that one skilled in the art can make and use the claimed invention, including the use of the elected biomarker, DMN, as classifier of osteoarthritis in a tested subject (e.g., relative to being classified as healthy) without the *a priori* need to know the direction or the level of differential expression that exists between subjects having osteoarthritis and healthy subjects.

Lack of directionality and/or magnitude in the specification as-filed does not render the claims of the present scope non-enabled. The Applicant has identified the elected gene DMN as being differentially expressed between individuals diagnosed as having osteoarthritis and healthy controls by demonstrating a statistically significant difference in the level of RNA, as described

in Example 24. The statistical significance of DMN's differential expression is evidenced by its p value of 4.14555E-05 as listed in Table 3O. Therefore, the Applicant has taught that there is a significant difference in differential expression for DMN between a population of individuals having osteoarthritis and a population of healthy individuals, and further has taught a method to compare the level of expression of DMN in a test individual with populations having osteoarthritis and populations of healthy subjects using methods to determine the similarity or difference in gene expression levels between the test subject and the tested control populations.

The office action objects to the recitation of the phrase "statistically significant". Support for reciting comparison of biomarker RNA levels of a test subject with those of control subjects having a disease (i.e. osteoarthritis) and with those of healthy control subjects, and determination of a statistically significant difference or similarity there between can be found in the published application (US 2004-0248170), for example at paragraph [0127] ("*When comparing two or more samples for differences, results are reported as statistically significant when there is only a small probability that similar results would have been observed if the tested hypothesis (i.e., the genes are not expressed at different levels) were true*"), and at paragraph [0128] ("*When comparing two or more samples for similarities, results are reported as statistically significant when there is only a small probability that similar results would have been observed if the tested hypothesis (i.e., the genes are not expressed at different levels) were true*"), respectively. Support for reciting classification of a test subject level relative to control levels can be found, for example, at claim 12 as originally filed ("*d) determining whether the level of said one or more gene transcripts of step a) classify with the levels of said transcripts in step b) as compared with the levels of said transcripts in step c)*"), at paragraph [0135] (relating to "*Methods that can be used for class prediction analysis*"), paragraph [0390] ("*Blood samples were taken from patients who were diagnosed with osteoarthritis and a specific stage of osteoarthritis as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease.*").

And, as particularly emphasized above, magnitude and/or directionality are not necessarily the key and/or exclusive determination that is needed to be made. Instead, "***[t]he most basic question one can ask in a transcriptional profiling experiment is which genes' expression levels changed significantly***." (Slonim DK, see above). Magnitude and/or

directionality are inherent features of the expression level of a gene which has been determined with statistical significance to be differentially expressed in diseased subjects versus healthy subjects. Accordingly, the Applicant believes that the specification establishes that there exists the requisite reliable association between DMN expression levels in subjects having osteoarthritis and healthy controls.

The office action states that it is clear that the applicant intends to use classification methods in order to provide a tool that is used as part of a diagnostic process, and such a use requires the knowledge of a reliable association underlying the classification.

The specification explicitly teaches the use of classification methods in at least paragraphs 0123-0126 and paragraph 0393 of the published instant application. In particular, paragraph 0135 describes methods that can be used for class prediction analysis, and paragraph 0393 describes that blood samples were taken from patients who were diagnosed with osteoarthritis as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease.

Specifically, paragraphs 0134-0136 of the published application state as follows:

[0134] As would be understood to a person skilled in the art, one can utilize sets of genes which have been identified as statistically significant as described above in order to characterize an unknown sample as having said disease or not having said disease. This is commonly termed "class prediction".

[0135] Methods that can be used for class prediction analysis have been well described and generally involve a training phase using samples with known classification and a testing phase from which the algorithm generalizes from the training data so as to predict classification of unknown samples (see for Example Slonim, D. (2002), Nature Genetics Supp., Vol.32 502-8, Raychaudhuri et al., (2001) Trends Biotechnol., 19: 189-193; Khan et al. (2001) Nature Med., 7 673-9.; Golub et al. (1999) Science 286: 531-7. Hastie et al., (2000) Genome Biol., 1(2) Research 0003.1-0003.21, all of which are incorporated herein by reference in their entirety).

[0136] As additional samples are obtained, for example during clinical trials, their expression profiles can be determined and correlated with the relevant subject data in the database and likewise be recorded in said database. Algorithms as described above can be used to query additional samples against the existing database to further refine the diagnostic and/or prognostic determination by allowing an even greater association between the disease and gene expression signature"

Thus, classification methods are a well known tool used in the art to refine algorithms to more accurately diagnose disease based on identified biomarkers. Paragraph 0393 of the instant specification further discloses the use of classification of a test sample of an individual to

classify said individual as having or not having osteoarthritis which can be done using the differentially expressed genes as shown in Table 3O, which includes DMN. In light of the disclosed use for Claim 71, drawn to a method of classifying expression of a gene encoding a DMN in a human test subject, Applicant contends claim 71 is fully enabled.

The comparison step of claim 71 is between a test subject and both healthy controls and controls with osteoarthritis. It does not compare other diseases. The use of the classification method is not disclosed to be an unequivocal diagnosis, but only one method in a battery of diagnostic assays to contribute to a diagnosis of osteoarthritis. Further, Claim 71 is not necessarily drawn to a method of distinguishing osteoarthritis from another disease such as renal cell carcinoma as suggested in the office action on page 9. In contrast, claim 71 is drawn to a classification method, which, as suggested in the office action when read in light of the specification, is designed to be used "to provide a tool that is used as part of a diagnostic process". As such, Claim 71 contains no resolution step of diagnosing osteoarthritis, and leaves open the use of other methods to confirm the diagnosis and/or the extent with which DMN is useful as a marker for osteoarthritis.

Regarding the concern of the office action that it is unknown and unpredictable whether DMN could be expressed in the blood of patients having another disease, (e.g., renal cell carcinoma, as suggested on page 9 of office action), Applicant notes that even the much litigated patented method claims of Metabolite Laboratories, Inc.'s U.S. Patent No. 4,940,658, ('658), include method steps which can be used to indicate a disease or disorder other than the disease/disorder recited. For example, Claim 13 of '658 is drawn to a method for detecting a deficiency of cobalamin or folate in warm-blooded animals by assaying a body fluid for an elevated level of total homocysteine, and is thus used as a method to detect vitamin deficiency. However, it was well known in the medical community before the filing of '658, that the assay for elevated homocysteine levels could signal an increased risk of heart disease. Despite much scrutiny for other reasons, claim 13 of '658 has not been invalidated as a result of other previously known use(s) of its claimed assay to provide a correlation to a second disease or disorder not recited in its claim 13.

The claims do not claim, seek, or even require the absolute diagnosis or classification of osteoarthritis. The use of a biomarker, as is used in the present claims, as a type of indicator of a disease is typically just one aspect, and typically an early aspect, of a multi-factorial process used

in diagnosing a person as having a particular disease of interest and can be useful in providing guidance in medical decisions regarding additional testing and treatment of a disease. The claimed methods are clearly not aimed at providing a definitive diagnosis of osteoarthritis, but rather a useful approach to provide assistance in the early stages of evaluating a patient for osteoarthritis, e.g., from a simple blood draw.

The office action indicates that the specification teaches that DMN is not differentially expressed in patients having osteoarthritis and hypertension, allergies, or with systemic steroids as compared with normal patients, and concludes that the gene is not significantly differentially expressed in all patients with osteoarthritis relative to healthy patients, page 7 of the office action. Further, the office action indicates that the disclosure does not provide a threshold of difference in DMN expression that would be "indicative of osteoarthritis", page 10 of the office action.

As noted in Stedman's 27th Edition Medical Dictionary, indication is not equated with diagnosis. The term indication is understood to mean "the basis for initiation of a treatment for a disease or of a diagnostic test" (see page 892). Even a diagnostic test is not considered to result in an absolute certainty of a diagnosis of disease – but rather is noted as "relating to or aiding in diagnosis". As noted in Harrison's Principles of Internal Medicine, Introduction to Clinical Medicine "the purpose of performing a test on a patient is to reduce uncertainty about the patient's diagnosis or prognosis and to aid the clinician in making management decisions" (Ch I, pg. 11). This same text further notes that while "a perfect test would have a sensitivity of 100% and a specificity of 100% and would completely separate patients with disease from those without it…there are no perfect tests, after every test is completed the true disease state of the patient remains uncertain" (Ch I, pg. 11). Accordingly, in view of the above, Applicant respectfully requests that the Examiner reconsider the nature and scope of the subject matter that is actually presently claimed. It is respectfully asserted, given that the nature and scope of the invention is directed to identifying a human test subject as being a candidate for having osteoarthritis (OA), classifying a human test subject as being more likely than not to have osteoarthritis (e.g., classifying a human test subject as being more likely to have osteoarthritis than to be healthy), or detecting expression of a DMN gene in a human test subject, one or ordinary skill in the art would not have required undue experimentation to make and/or use the present invention.

The office action indicates that some claims recite controls that do not have osteoarthritis. In the interest of advancing prosecution, Applicant has amended the claims to specify that these controls are healthy controls. Specifically, Applicant has cancelled claims 63 and 64, without prejudice, and changed the dependency of claim 65 to depend from claim 62. All pending claims that require comparison with a negative control now specify that the negative control is healthy.

The office action states on page 6, that there is no universally accepted level of statistical significance. Accordingly, Applicant has amended claim 71 to specify that the required statistical significance have a p value of less than 0.05.

The Office Action also suggests that field of analyzing expression profiles remains highly unpredictable years after the filing of the instant application, (pages 8-10 of the Office Action). The Applicant submits that the differential expression of DMN as between subjects having osteoarthritis and subjects not having osteoarthritis is, in fact, predictable. As stated in the Manual of Patent Examining Procedure at 2164.03: the "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. In the instant application, the disclosed result is a statistically significant differential expression in the level of DMN RNA as between subjects having osteoarthritis and subjects not having osteoarthritis, the statistically significant difference having a p value < 0.05, as indicated in Table 3O of the instant specification.

The Office Action states on pages 8 that Lee teaches that data obtained from gene chips must be replicated in order to screen out false positive results; on page 10 that Cheung et al. (2003) teaches that there is natural variation in gene expression amongst different individuals; on page 11 that Wu et al (2001) teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, and that the conclusions that can be drawn from a given set of data depend on the particular choice of data analysis; and also on page 11 that Newton et al. (2001) teaches that a replication of data is required for validation.

Applicant respectfully disagrees with the contention based on Wu et al. that expression data needs to be interpreted in view of other biological knowledge. Differential gene expression which is reproducible, and is correlated with the state of health or disease of the individual may not necessarily result directly from the state of disease of the individual. Rather these changes in expression may simply represent a downstream side-effect of pathogenic processes, and it is not necessary that the biological relevance of the data be known to allow this difference in

expression to be useful as a biomarker. For example prostate-specific phosphatase and prostate-specific antigen (PSA) were long used as biomarkers without an understanding of their function, as evidenced by Chu TM, 1990, Prostate cancer-associated markers. Immunol. Ser. 53:339-56; and Diamandis EP., 2000, Prostate-specific antigen: a cancer fighter and a valuable messenger? Clin Chem. 46:896-900), of record.

The Examiner also argues, on the basis of post-filing art of Wu (2001) and Newton (2001), that many factors may influence the outcome of the data analysis and notes that conclusions depend on the methods of data analysis. While considerations such as variability, and normalization are of importance, these considerations are well understood by a person skilled in the art and have been applied for many years to permit development of biomarkers which are indicative of disease. These challenges are well understood, as are the routine experiments required to exemplify statistically significant differences in populations.

Applicant notes that the results disclosed by Cheung *et al.* cannot be reliably extrapolated to primary blood samples since the lymphoblastoid cells employed by Cheung *et al.* are significantly modified relative to primary blood cells, due to being cultured cell lines generated by immortalization of primary human cells derived from "CEPH" families, as indicated in Reference no. 10 of Cheung *et al.* (Dausset *et al.*, 1990. Genomics 6:575;) at p. 575, right column, 1st paragraph. Applicant notes that immortalized cultured cell lines such as the lymphoblastoid cells taught by Cheung *et al.* undergo significant genetic modification such as strong genome-wide demethylation (refer, for example, to Vilain *et al.*, 2003. DNA methylation and chromosome instability in lymphoblastoid cell lines. Cytogenet Cell Genet. 90:93) of record, as a result of extensive *in-vitro* culturing in the absence of immune or apoptotic mechanisms which function to eliminate mutated cells in the body. As such, immortalized CEPH lymphoblastoid cells may represent a particularly unsuitable cell type for modeling gene expression variability in primary blood cells.

The office action, in response to Applicant's assertion that the results of Cheung et al. can not be reasonably extrapolated to primary blood samples since Cheung et al. use cultured cell lines, contends that this is "irrelevant to the Cheung et al. which is that among individuals (in this case cell lines) there is a natural variability in gene expression for any particular gene", see page 21 of the office action. Applicant again emphasizes that the term "individual" refers to primary blood samples composed of highly heterogenous mixture of cell types, not to clonal cultured cell

lines, and requests support from the Examiner demonstrating that the variability of among cultured cell lines is analogous to the variability of blood samples from individuals in general and in particular for the gene DMN.

To the extent that Cheung et al. could still be considered to suggest that larger populations of diseased and control populations may be useful to determine what level of differential expression is indicative of disease amongst the population at large, the Applicant submits that the extension of the experiments as outlined in the specification to additional individuals is merely routine. As is noted in Re Wands "*even a considerable amount of experimentation is permissible to practice the claimed methods, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.*" (Re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

As such the Applicant believes there is sufficient guidance provided by the specification that DMN gene is differentially expressed between human individuals who are healthy as compared to those having osteoarthritis, and that the art is sufficiently predictable such that the amount of experimentation to perform the instantly claimed methods of diagnosing osteoarthritis and identifying candidate subjects who may have osteoarthritis is not undue. In light of the amendments and above remarks, the Applicant contends that the claims are fully enabled, and respectfully requests reconsideration and withdrawal of the instant rejection.

Claim Rejections - 35 USC § 102

Claims 59, 61, 62, 63, 64, 65, 70, 72, 73 and 77 are rejected under 35 U.S.C. 102(a) and (b) as being unpatentable over Chittenden (2002 thesis).

Applicant respectfully traverses on the grounds that Chittenden does not teach every limitation of the claims. Specifically, Applicant contends that Chittenden does not teach a method of detecting expression of DMN in blood. The office action contends that is an inherent property of the array HG-U133A that it contains probes to DMN. However, the office action provides no evidence that DMN was actually detected by Chittenden, and further admits that Chittenden does not specifically discuss DMN expression.

The office action asserts that DMN would have inherently been detected in the blood of healthy controls by the hybridization and array reading methods of Chittenden. Applicant notes

that this is an unverified assumption by the office action, and makes the assumption that there was no technical difficulties with the hybridization of nucleic acid derived from the blood sample to the DMN probe on the array. Without a specific teaching that DMN was detected in human blood, Chittenden does not anticipate the instant claims.

Reconsideration and withdrawal of the instant rejections is respectfully requested.

Claim Rejections - 35 USC § 103

Claims 59, 61-65, 70, 71, 72, 73, 74, 75 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carmen et al. (US 2003/0170743), in view of Sharma et al. (WO 98/49342).

Applicant respectfully traverse on the grounds that the combination of references does not arrive at the claimed invention.

Carmen et al. teaches a method of detecting RNA encoded by a DMN gene using an Affymetrix chip U95V2 A, B and C chips. However, Carmen et al. does not teach looking for DMN expression in blood. Applicant notes that neither Carmen et al. nor the Affymetrix data sheet teach any relationship between DMN expression in blood and osteoarthritis. Thus the cited references would only be combined by one of skill having the benefit of Applicant's specification, and as such is hindsight.

The office action contends that one of skill would have been motivated to modify the methods of Carmen et al. to 1) look for DMN expression in blood and 2) to incorporate the Affymetrix gene chip, by Sharma et al.'s teachings that disease exerts a global effect on individuals and that this effect can be measured by gene expression in blood.

Applicant submits that the generic teaching by Sharma is not sufficient motivation to apply the teachings of Carmen et al. to detect expression of a DMN gene in blood of a human test subject having osteoarthritis because Sharma et al. provides no substantive scientific basis to predictably arrive at the claimed invention of identifying a DMN gene as a candidate marker for osteoarthritis based on its specification.

The Office Action indicates that Sharma et al teaches: "From the very early stages of diseases caused by infections, toxic substances, ageing or other conditions changing the quality of life of living eukaryotic organisms, the whole organism responds to the changed condition", page 10, 4th full paragraph, WO 98/49342

and

"The invention is a quick and precise method for the diagnosis of ***any disease or condition that leads to alterations in the activity of genes*** in a pattern which is specific to any particular condition of the organism under observation", emphasis added, page 10, 2nd full paragraph, WO 98/49342.

The latter paragraph indicates that Sharma's teachings do not necessarily apply to every disease, but only to those disease(s) that "leads to alterations in the activity of genes in a pattern which is specific to any particular condition of the organism under observation". Further, Sharma et al. provides not a single piece of preliminary data of differential expression in whole blood of any RNA with respect to disease, including osteoarthritis.

Accordingly, Applicant contends that neither the prophetic nor the non-prophetic working examples of Sharma et al. provide sufficient motivation for one of skill reading Sharma's WO document to modify the methods of Carmen et al. by substituting blood as the tissue source to identify markers useful in identifying/classifying osteoarthritis.

Applicant respectfully traverses the rejection, on the grounds that one guideline published by the USPTO for determining obviousness after KSR (Federal Register, Vol. 72, No. 195; October 10, 2007), is that a simple substitution of one known element for another to obtain predictable results. As discussed above, Sharma et al.'s prophetic examples do not provide a reliable scientific basis for practicing the claimed methods of identifying biomarkers useful in detecting osteoarthritis in blood with a reasonable expectation of success.

Thus, it would not have been predictable based on the cited art to one of skill in the art at the time the invention was made, who was considering combining the methods of Carmen et al. with Sharma et al. by using the Affymetrix gene chip array to identify DMN as a candidate biomarker for osteoarthritis, that such a combined method would be successful and/or predictably arrive at the claimed invention. In the absence of predictability ***at the time of the invention*** in arriving at the claimed invention by substituting blood as the source of DMN RNA in the methods of Carmen et al., one of skill would not have had a reasonable expectation of

success in practicing the claimed invention, and thus no prima facie case of obviousness can be made. Reconsideration and withdrawal of the instant rejection is respectfully requested.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. No new matter is added. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

Date: August 26, 2008

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